Non-Mosaic Tetrasomy 9p in An Infant With Multiple Congenital Anomalies

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Supernumerary isochromosomes resulting in autosomal tetrasomy are rare and have been described for 12p, 18p and 9p. To date, approximately 30 patients have been described with a tetrasomy 9p, majority of cases being mosaics. We present a new case of non-mosaic i(9p) that presented to us early in infancy with significant dysmorphological features including severe retardation, hypertelorism, cleft lip and palate, micrognathia and low set malformed ears. Skeletal abnormalities were loss of some of the phalanxes, hypoplastic nails with mild syndactyly, limb contractures and dislocated hibs. The main difference between mosaic and non-mosaic infants is the poorer prognosis of non-mosaics. The infant died at 28th day of age, three days later of hospitalization.

Karyotype analysis of blood lymphocytes indicated an additional marker as an isochromosome in the size of E-16. The origin and structure of this additional marker could not be determined by chromosome banding. Application of fluorescence in situ hybridization identified the origin of marker chromosome as isochromosome 9p, demonstrating the effectiveness of molecular cytogenetic investigation in the diagnosis of structural and numerical chromosomal abnormalities.

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Supernumerary isochromosomes causing autosomal tetrasomy are rare and recorded isochromosomes include i(5p), i(8p), i(9p), i(12p), i(18p), i(21q), i(22q), and i(Xq). Mosaicism is very frequent, implying that a postzygotic origin is common.

To date, only about 38 cases of tetrasomy 9p due to the presence of supernumerary isochromosome 9p have been reported, most of them in mosaic status.[1,2]

Tetrasomy of the short arm of chromosome 9 constitutes a clinically recognizable chromosomal syndrome.[3] Most children with tetrasomy 9p have characteristic craniofascial abnormalities, generalized hypotonia, moderate to severe pshycomotor retardation, congenital heart disease, renal anomalies and foot deformities.[2] Phenotype varies in severity from neonatal death to mild developmental delay and minor anomalies. Mosaicism has effects on the severity of phenotype.

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We present a further case of non-mosaic tetrasomy 9p with severe abnormalities and short survival .

Case Report

The male patient was born to a 35 year-old, gravida 5, para 5 woman from a non-followed up pregnancy at term. Delivery was performed by spontaneous vaginal delivery at home conditions. He case was referred to us because of multiple malformations at 25th days of age.

Body weight was 1,800 g (below 3rd centile), length 47 cm (below 3rd centile), and head circumference 33 cm (below 3rd centile).

He had severe retardation, hypotonia, marked hypoplasia of muscles and umblical hernia. Craniofacial findings included a prominent forehead, prominent occiput, hypertelorism, prominent nasal bridge with beaked nasal tip, cleft lip and palate, micrognathia and low set malformed ears (Fig.1).

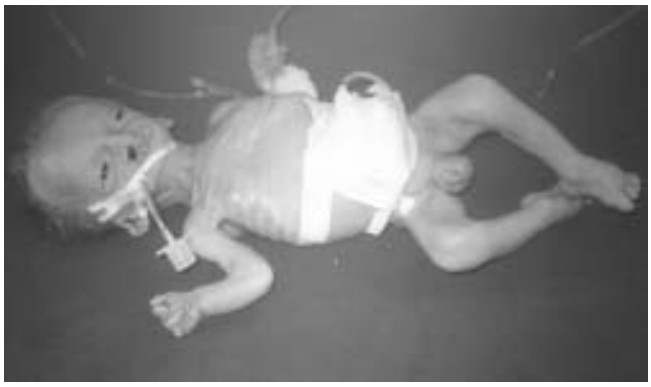

Figure 1: Overall appearance of the patient with multiple malformations

Skeletal abnormalities were loss of some of the distal phalanxes, short fingers and thumbs, hypoplastic nails with mild syndactyly. He had flexion contractures of both elbows, dislocated hips, bilateral metatarsus abduction deformity, limited dorsoflexion of ankle and pes cavus.

Genitourinary system examinations showed hydrocele, cryptoorchidism, and pelvicalixeal dilatation on ultrasound. Hydrocephaly and intraventricular hemorrhage (GradeIII) was detected as CNS abnormality.

Karyotype analysis of blood lymphocytes indicated an additional marker as an isochromosome in all of the cells examined. The origin and structure of this additional marker could not be determined by GTG-banding. Application of FISH, using wcp 9 (Oncor) probe, identified the origin of extra chromosome as isochromosome 9p. Resampling or sampling of other tissues could not be performed because the patient had died soon after first sampling.

Discussion

We present a non-mosaic case of tetrasomy 9p diagnosed by using FISH. The clinical features of our case are also helpful for clinical diagnosis. Tetrasomy 9p syndrome is not a well recognizable clinical entitiy as trisomy 9p yet. However, as the larger number of cases reported a clear phenotype is emerging. Predominant phenotypic findings of previously reported mosaic and non-mosaic tetrasomy 9p cases are given in Table-1 in comparison with our case.

Table-1: Previously reported features of mosaic and non mosaic cases of tetrasomy 9p compared with features of present case (: <40%, **: 40-80%, ***: >80%)*

Clinical findings	Mosaics (%)	Non mosaics(%)	Present case
IUGR / SGA	*	**	+
Postnatal growth failure	**	***	+
Developmental delay	***	***	+
Early death	-	**	+
Brachycephaly/microcephaly	*	*	-
Short neck/excess nuchal skin	**	**	-
Micro / retrognathi	***	**	+
Cleft Lip / Cleft Palate	**	***	+
Hypertelorism	**	***	+
Prominent nasal bridge / bulbous or beaked nose	**	**	+
Ear anomaly	**	***	+
Limb contractures /joint dislocation	*	**	+
Other limb defects	***	***	+
CNS anomaly	***	**	+
CV anomaly	**	**	-
Renal anomaly	*	**	+
Abnormal genitalia	*	**	+

The phenotype of tetrasomy 9p cases varies in severity from mild developmental delay with minor anomalies to prenatal death, probably depending on the size of the tetrasomic region and the degree of mosaicism.[4] According to Schinzel, patients with mosaicism for an extra chromosome 9p have distinctly milder phenotype than without mosaicism.[5] Most authors agree that mosaicism has an effect on mortality rate. Some reports indicated that the main difference between mosaics and non-mosaics is the poorer prognosis of non-mosaics.[6,7] Tetrasomy 9p was non-mosaic in our case and he died early in infancy, 28th day of birth, supporting this idea.

Three types of tetrasomy 9p, based on the nature of the isochromosome with break point at p10, a small amount of heterochromatic region extending to 9q12 or 13 and a larger portion extending to 9q21 or 9q22 were included, can be seen in the literature.[2,3,8] However, some of these authors found no correlation between the nature of the isochromosome and the phenotype. Our case showed a non-mosaic supernumerary isochromosome with no portion of long arm of chromosome 9.

Tissue-limited mosaicism may be another factor that contributes to the phenotypic variation. Tetrasomy 9p, like tetrasomy 12p in Pallister-Killian Syndrome, shows a tendency for tissue limited mosaicism. However, unlike tetrasomy 12p, which occurs in skin but very rare in blood, tetrasomy 9p appears predominantly in the blood cultures, often at a lower frequency or absent in skin, amniotic or chorionic villous cell culture.[3] Tissue-limited mosaicism cannot be ruled out in cases where only lymphocytes were analyzed as in our case.

Tissue-limited mosaicism in tetrasomy 9p sometimes causes the anomaly undetectable by CVS or amniocentesis.[2,3] For this reason prenatal diagnosis may be difficult. Reports on prenatal diagnosis of tetrasomy 9p were limited in the literature.[1,9] There are some common findings of tetrasomy 9p on ultrasound, which can be confirmed prenatally such as IUGR, cleft lip/palate, central nervous system malformations, genitourinary or renal anomaly and skeletal abnormalities.[1,7,10] Interestingly these abnormalities are also suggestive of trisomy 13. Therefore, when trisomy 13 is suspected but not confirmed using standard prenatal FISH, tetrasomy 9p diagnosis should also be suspected.

We present a pattern of dysmorphic clinical features of a new case of non-mosaic tetrasomy 9p in order to contribute a better description and early diagnose of the syndrome.

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